

Safety and Side Effects of Ayahuasca in Humans—An Overview Focusing on Developmental Toxicology

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Abstract—Despite being relatively well studied from a botanical, chemical, and (acute) pharmacological perspective, little is known about the possible toxic effects of ayahuasca (an hallucinogenic brew used for magico-ritual purposes) in pregnant women and in their children, and the potential toxicity of long-term ayahuasca consumption. It is the main objective of the present text to do an overview of the risks and possible toxic effects of ayahuasca in humans, reviewing studies on the acute ayahuasca administration to humans, on the possible risks associated with long-term consumption by adults and adolescents, and on the possible toxic effects on pregnant animals and in their offspring. Acute ayahuasca administration, as well as long-term consumption of this beverage, does not seem to be seriously toxic to humans. Although some nonhuman developmental studies suggested possible toxic effects of ayahuasca or of some of its alkaloids, the limited human literature on adolescents exposed to ayahuasca as early as in the uterus reports no serious toxic effects of the ritual consumption of the brew. Researchers must take caution when extrapolating nonhuman data to humans and more data are needed in basic and human research before a definite opinion can be made regarding the possible toxic effects of ayahuasca in pregnant women and in their children.

Keywords—ayahuasca, hallucinogens, psychopharmacology, tolerability, toxicology

Ayahuasca is a psychoactive hallucinogenic plant preparation, which has as its main ingredient the Amazonian jungle vine *Banisteriopsis caapi*, which is rich in β -carbolines, especially harmine, tetrahydroharmine (THH) and harmaline (usually present only in trace amounts) (dos Santos 2011a; Riba 2003; Ott 1994; Schultes & Hofmann 1992; Schultes 1986). Ayahuasca can be prepared with *B. caapi* alone or by adding various admixtures plants to the liana in the beverage preparation. Among these other plants, one of the main ingredients is the shrub *Psychotria viridis*, which is rich in the serotonin_{2A/2C/1A} receptor agonist hallucinogen *N,N*-dimethyltryptamine

(DMT) (dos Santos 2011a; Riba 2003; Ott 1994; Schultes & Hofmann 1992; Schultes 1986). β -Carbolines in ayahuasca (i.e., harmine, THH and harmaline) are reversible inhibitors of the enzyme monoamine oxidase A (MAO-A), which is involved in DMT metabolism. In ayahuasca, compounds that are inhibitors of MAO-A from *B. caapi* inhibit the metabolism of DMT in the gut and thereby allow it to reach the central nervous system (dos Santos 2011a; Riba 2003; Riba et al. 2003).

Ayahuasca has been used by dozens of indigenous groups from the Northwestern Amazon for ritual purposes at least for centuries. Ayahuasca has also been used by *mestizo* populations in Amazonian countries like Peru and Colombia for decades (Luna 2011). The Brazilian ayahuasca religions Santo Daime, União do Vegetal and Barquinha, which use ayahuasca ritually, are now present in many parts of the world (Labate, Rose & dos Santos 2009).

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There is increasing interest in the effects of ayahuasca on humans, especially in adolescents and children, and also on the therapeutic potentials of this beverage. It seems an appropriate moment to review the safety and toxicological aspects associated with the acute administration and also with the long-term consumption of ayahuasca.

The main objective of the present work is to provide an overview of the toxicological aspects of ayahuasca in humans. Also, the possible relevance of preclinical studies on developmental toxicology to the human ritual context of ayahuasca consumption will be discussed.

MATERIAL AND METHODS

A bibliographical research was performed searching for ayahuasca research conducted in humans until January of 2013. Preference was made for including in this review double-blind placebo-controlled randomized clinical trials of acute ayahuasca administration, but studies that did not include a nondrug (placebo) condition were also included. Psychological, neuropsychological and psychiatric evaluations of long-term ayahuasca consumption by adolescents and adults were also reviewed. Another bibliographical research, also conducted until January of 2013, was performed for preclinical studies of developmental toxicology involving ayahuasca or some of its isolated alkaloids. For both bibliographical researches, study languages were limited to Portuguese, English and Spanish. Article research was performed using the PubMed and SciELO (Brazilian) databases, specialized books and book chapters, as well as the relevant bibliographies extracted from research papers, books and book chapters.

RESULTS AND DISCUSSION

Studies of Acute Ayahuasca Administration

The clinical pharmacology of acute doses of ayahuasca has been well characterized by the team of Dr. Jordi Riba in the Hospital de la Santa Creu i Sant Pau, in Barcelona, Spain. This team has conducted a series of controlled clinical trials of acute ayahuasca administration. The ayahuasca used in the studies by Riba and colleagues was prepared and imported from Brazil and used in the clinical trials as encapsulated freeze-dried material in which doses used ranged from 0.5 to 1 mg DMT/kg body weight. Studies included single- (Riba et al. 2001) and double-blind (dos Santos et al. 2012, 2011; Barbanoj et al. 2008; Riba et al. 2006, 2004, 2003, 2002; Riba, Rodríguez-Fornells & Barbanoj 2002; Yritia et al. 2002) crossover placebo-controlled clinical trials using a single ayahuasca dose (dos Santos et al. 2011; Barbanoj et al. 2008; Riba et al. 2006, 2004, 2003, 2002, 2001; Riba, Rodríguez-Fornells & Barbanoj 2002; Yritia et al. 2002) or two repeated doses (dos Santos et al. 2012).

Jordi Riba's group investigated the impact of acute ayahuasca administration to healthy volunteers on neurophysiological (dos Santos et al. 2012, 2011; Barbanoj et al. 2008; Riba et al. 2004, 2002; Riba, Rodríguez-Fornells & Barbanoj 2002), neuroendocrine (dos Santos et al. 2012, 2011), cardiovascular (dos Santos et al. 2012; Riba et al. 2003, 2001), autonomic (dos Santos et al. 2012, 2011), biochemical (Riba et al. 2001) and immunological (dos Santos et al. 2012, 2011) measures. Pharmacokinetic/metabolism (Riba et al. 2003; Yritia et al. 2002; see also McIlhenny et al. 2012, 2011; Riba et al. 2012) and neuroimaging studies (Riba et al. 2006) were also performed.

All these studies provide evidence that acute administration of ayahuasca in the clinical setting to healthy volunteers is safe, presenting an acceptable tolerability (reviewed in dos Santos 2011a; Bouso & Riba 2011; Riba & Barbanoj 2011, 2005; dos Santos 2010a; Gable 2007; Riba 2003).

The subjective effects of ayahuasca included significant perceptual, cognitive and affective modifications. A time curve of DMT plasma levels, which fit with the overall duration and peak values of subjective effects, was described (Yritia et al. 2002; Riba et al. 2003), as well as an increased urinary excretion of normetanephrine, a methylated breakdown product of norepinephrine (Riba et al. 2003). The increase in normetanephrine is in line with MAO inhibition. Blood analyses were without any evidence of clinically relevant alterations in hematological indices or biochemical indicators of liver function or other standard analytical parameters (cellular counts, plasma bilirubin, and hepatic enzymes) (Riba et al. 2001).

Ayahuasca produced significant and dose-dependent modifications of brain electrical activity (electroencephalography, EEG), which were more intense and longer lasting as the dose increased. Specifically, ayahuasca produced a relative power increase in the beta band (dos Santos et al. 2012, 2011; Riba et al. 2002). Ayahuasca also produced a decremental effect on sensory gating as measured by P50 suppression (Riba, Rodríguez-Fornells & Barbanoj 2002).

The differential involvement of cortical brain regions in the EEG effects of acute ayahuasca administration was analyzed by means of low-resolution electromagnetic tomography (LORETA) (Riba et al. 2004). This study reported that ayahuasca decreased power density predominantly over the temporo-parieto-occipital junction, temporomedial cortex and in frontomedial regions. These areas comprise the somatosensory, auditory and visual association cortices, the temporo-parietal association cortex, and also paralimbic structures, with relevant roles in emotion and memory processes.

Ayahuasca administration led to significant activation of frontal and paralimbic brain regions measured by means of single photon emission tomography (SPECT). Increased blood perfusion was observed bilaterally in

the anterior insula/inferior frontal gyrus, with greater intensity in the right hemisphere, and in the anterior cingulate/frontomedial cortex of the right hemisphere, areas previously implicated in somatic awareness, subjective feeling states, and emotional arousal. A smaller cluster was found in the ventral anterior cingulate/subcallosal gyrus. Additional increases were observed in the left amygdala/parahippocampal gyrus, a structure also involved in emotional arousal (Riba et al. 2006).

Barbanoj and colleagues (2008) reported that ayahuasca did not induce any subjectively perceived deterioration of sleep quality or polysomnography-measured disruptions of sleep initiation or maintenance. Ayahuasca inhibited REM sleep, decreasing its duration.

Moderate increases in systolic blood pressure, diastolic blood pressure and heart rate were also reported (dos Santos et al. 2012; Riba et al. 2003, 2001), which led Riba and colleagues to conclude that ayahuasca poses only a moderate risk from the cardiovascular point of view when administered to healthy volunteers. Nevertheless, Riba and Barbanoj (2005) reported that in their pilot and final study combined, two volunteers showed systolic blood pressure values above 140 mm Hg at some point and four showed diastolic blood pressure values above 90 mm Hg, the diagnostic criteria for hypertension. One volunteer showed heart rate values above 100 bpm, the diagnostic criterion of tachycardia.

Plasma levels of prolactin, cortisol, and growth hormone showed increases after ayahuasca and autonomic measures (temperature, respiration, pupillary measures) were moderately modified. Immunological effects of ayahuasca included time-dependent modifications in lymphocyte subpopulations: percent CD4 and CD3 were decreased, whereas natural killer cells were increased (dos Santos et al. 2012, 2011).

Nausea and vomiting were the most frequently reported adverse effects found in the studies by Riba and colleagues (dos Santos et al. 2012; Riba & Barbanoj 2005; Riba et al. 2001). The most distressing event reported in the studies by Riba and colleagues (2001) was experienced by one volunteer during the pilot study after receiving the medium 0.75 mg/kg dose. The participant experienced an intensely dysphoric reaction with transient disorientation and anxiety. Verbal support was sufficient to get him through this state, which lasted around 20 minutes. His displeasure with the experience led him to voluntarily withdraw from the study. Riba and Barbanoj (2006) commented on a case of a volunteer who reported feelings of suspiciousness and menace after taking ayahuasca in the laboratory setting. According to the authors, all these signs disappeared completely after the expected time of action of ayahuasca and no medical intervention was needed.

Prado and colleagues (2009) conducted a double-blind study on a group of regular ayahuasca users

who underwent functional magnetic resonance imaging (fMRI) scans during the performance of a verbal fluency task. After ayahuasca, fMRI data—independent from the task—showed activation bilaterally in anterior and posterior cingulate, superior, middle and medial frontal gyrus, middle and superior temporal gyrus and precuneus. Task-dependent fMRI data showed decreased activation of areas involved in language processing (Broca's area/regions of the frontal, temporal, occipital and parietal lobes/limbic areas/thalamus), and also activation in other areas (cingulate/temporal lobe). Perceptual and thought alterations, mood/affect elevation, with no loss of contact with reality were reported, and no serious adverse effects were reported.

Several studies that did not include a nondrug (placebo) condition also presented data suggesting safety and acceptable tolerability after acute ayahuasca administration. de Araújo and colleagues (2012) conducted a study using fMRI to explore the neural basis of the visual imagery produced by ayahuasca in frequent ayahuasca users. Ayahuasca produced increases in the activation of several occipital, temporal and frontal areas. In the primary visual area, the effect was comparable in magnitude to the activation levels produced by a natural image with the eyes open, and was specifically correlated with the occurrence of individual perceptual changes measured by psychiatric scales. The activity of ayahuasca was shown in areas involved in episodic and working memory, the processing of contextual associations, intentional prospective imagination, and the processing of information from internal sources.

Barbosa and colleagues (2005) investigated the short-term psychological and psychiatric after-effects in naïve ayahuasca users, describing a significant reduction in the intensity of minor psychiatric symptoms in the week after the ayahuasca experience.

Stuckey and colleagues (2005) recorded electroencephalographic measures in two experienced ayahuasca consumers and reported increased global gamma coherence, and Frecska and colleagues (2004, 2003) reported that acute ayahuasca administration to individuals who were participating in ayahuasca ceremonies produced several effects on binocular rivalry, which was interpreted as indicating interhemispheric fusion.

Callaway and colleagues (1999, 1996) measured the acute subjective, neuroendocrine, cardiovascular and autonomic impact of ayahuasca administration to long-term users of the brew, using a standard dose of ayahuasca of 2 ml/kg body weight. The overall pattern of subjective and physiological effects was similar to the reports by Riba and coworkers, presenting increases in prolactin, cortisol and growth hormone levels and on cardiovascular and autonomic measures. Pomilio and colleagues (2003, 1999) reported similar effects on subjective and neuroendocrine measures after acute ayahuasca administration.

In an exploratory study of acute ayahuasca administration to three depressed females participants (Osório et al. 2011; see below), no serious adverse reactions were reported, suggesting good tolerability for ayahuasca in this group of patients.

Studies of Long-Term Ayahuasca Consumption by Adults

There appears to be an overall good tolerability for long-term ayahuasca consumption. The available scientific literature suggests that there is no evidence of physiological toxicity in long-term consumers of ayahuasca, and that this population does not present evidence of psychological, neuropsychological or psychiatric harm (Bouso et al. 2012, 2011; Fábregas et al. 2010; Barbosa et al. 2009; Halpern et al. 2008; Andrade et al. 2004; Grob et al. 1996; Callaway et al. 1994; see for review Barbosa et al. 2012; Bouso & Riba 2011; dos Santos 2010a; Gable 2007). The volunteers evaluated in these investigations, which included many long-term members of Brazilian ayahuasca religions like Santo Daime, União do Vegetal and Barquinha, have been consuming ayahuasca for several years, sometimes for several decades, without any apparent harm.

The incidence of psychopathology in this population appears to be low, although some cases have been published describing the occurrence of psychotic manifestations that can persist after the expected effects of ayahuasca (dos Santos & Strassman 2011; Lima & Tófoli 2011; Lima et al. 2002; see for review Bouso & Riba 2011; dos Santos 2010a; Gable 2007). Nevertheless, according to the scientific evidence, these psychotic-like adverse reactions seem to be a rare outcome following ayahuasca ingestion.

Ayahuasca, Pregnant Women and Adolescents

The use of ayahuasca by pregnant women, and the possible toxic effects in their children, is a topic that has not been much explored. The only studies that evaluated some of these aspects concluded that adolescents exposed to ayahuasca in various stages of their development, including in the uterus and throughout childhood and adolescence, were normal from a psychiatric, psychological and neuropsychological perspective (da Silveira et al. 2005; Dobkin de Rios et al. 2005; Doering-Silveira et al. 2005a, b). Furthermore, it must be acknowledged that there is no scientific publication reporting any toxic effects of ayahuasca in pregnant women or in children born from these women, despite the at least centuries-old human ritual consumption of ayahuasca (Labate 2011).

Ayahuasca's Potential for Causing Life-Threatening Adverse Reactions

There are some rare media reports associating ayahuasca with life-threatening adverse reactions (e.g., coma) and also with fatal adverse reactions (América Noticias 2012; El Comercio 2012; Farberov 2012; Johnson

2012; Kovner 2012; Mason 2012; Perú21 2012; Roberts 2012; RPP Noticias 2012; Cárdenas 2011; Colombia Reports 2011; El Espectador 2011; La Gaceta 2011; La Republica 2011; Perú21 2011; Vanguardia 2011; CityTv 2010; El Comercio 2010; Gomes 2010; La FM 2010; La Republica 2010; RPP Noticias 2010; Vera 2010; Neto 2009; UOL Notícias 2009).

Nevertheless, a causal role for ayahuasca is not clear in many of these cases, since no forensic analysis was made and only speculative explanations are given (e.g., “died after experiencing convulsions,” “fulminant heart attack” that “torn apart the aortic artery”). (for a critical discussion of these cases, see dos Santos In press[a]). It also must be acknowledged that all these cases were reported in the nonscientific literature, and that dramatic media reports only help to obscure possible causal relationships between ayahuasca and potential life-threatening adverse reactions.

There are some published articles associating β -carbolines, tryptamines and ayahuasca with potential life-threatening adverse reactions and even fatal outcomes (Sklerov et al. 2005; Brush, Bird & Boyer 2004; Warren 2004). Nevertheless, none of these reports is about ayahuasca per se, so they will not be further discussed in the present text (for a critique of one of these studies, see Callaway et al. 2006; for a critical discussion of all the cases, see dos Santos In press [a]), so they will not be further discussed in the present text. Moreover, the bibliographical review failed to find any case published in the scientific literature of any life-threatening or lethal adverse reactions caused by ayahuasca per se.

Ayahuasca and Possible Chemical Interactions

The combination of MAO inhibitors such as some β -carbolines with monoaminergic and serotonergic substances like selective serotonin reuptake inhibitors, tryptophan or antidepressives in general could potentially produce the serotonin syndrome (dos Santos In press[b]; Frecska 2007; Boyer & Shannon 2005; Callaway 2002; Callaway & Grob 1998; Hilton, Maradit & Möller 1997).

Ginseng, St. John's wort, dextromethorphan, amphetamine or the empathogen-entactogen 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) could also produce a potentially dangerous interaction when using ayahuasca (Pilgrim et al. 2012; Frecska 2007; Silins et al. 2007; Boyer & Shannon 2005; Vuori et al. 2003). Also important is the observation that harmine is a selective inhibitor of the human cytochrome P450 isozyme 2D6 (CYP2D6), which also metabolizes harmaline (Zhao et al. 2011; Wu et al. 2009; Callaway 2005; Riba et al. 2003; Yu et al. 2003). The addition of drugs that inhibit cytochrome isoform CYP2D6 to the therapeutic use of selective serotonin reuptake inhibitors has been associated with the serotonin syndrome (Boyer & Shannon 2005).

The combination of foods containing tyramine and MAO inhibitors can potentially lead to hypertension (dos

Santos In press; Frecska 2007; Yamada & Yasuhara 2004; Youdim & Weinstock 2004), and drugs like psilocybin, mescaline and cannabis can also produce interactions with ayahuasca (dos Santos 2011b; Ott 1994).

Therapeutic Potentials of Ayahuasca

There is anecdotal evidence that ayahuasca has therapeutic potential for treating several diseases including substance dependence, depression and several psychological disorders, and also for curing cancer (e.g., Topping 1998). On the other hand, experimental studies for testing these potential effects are almost nonexistent.

Recent preclinical and human studies present evidence that ayahuasca or some of its alkaloids have anxiolytic and antidepressive effects (Réus et al. 2012, 2010; dos Santos et al. 2007; Fortunato et al. 2010a, 2010b, 2009; see for a review Osório et al. 2011). An exploratory study involving three female participants with a clinical diagnosis of recurring depressive disorder and current mild/severe depressive episode without psychotic symptoms was conducted by Osório and collaborators (2011). The subjects had not been in treatment with antidepressants for two weeks and received a single oral dose of ayahuasca. A significant decrease in the scores of the Hamilton Depression Scale was reported starting at 40 minutes after ayahuasca intake. Sustained reduction in the scores of depressive symptoms was observed from day 1 ($\pm 79\%$ in relation to baseline) to day 14 ($\pm 66\%$ below baseline), when an expressive increase in depressive symptoms was seen towards baseline levels.

In the case of drug dependence, there is preclinical evidence suggesting that harmine, a major ayahuasca alkaloid, could have therapeutic potentials for treating this disorder (Brierley & Davidson 2012a, 2012b; Owaisat, Raffa & Rawls 2012; Aricioglu-Kartal et al. 2003). Moreover, anecdotal evidence of the possible therapeutic role of ayahuasca in treating drug dependence is abundant, and several clinics exist which offer ayahuasca treatments for substance dependence (Fernández & Fábregas In press; Labate et al. In press; dos Santos, Moraes & Holanda 2006; for a review see Labate et al. 2010).

Ayahuasca and Preclinical Developmental Toxicology

Early and modern studies. Studies conducted during the 1960s and 1970s reported some toxic analyses of the ayahuasca alkaloids in pregnant animals (Halky 1974; Kamel, Ibrahim & Hamza 1971; Poulson & Robson 1963; for a review see dos Santos 2010b). Poulson and Robson (1963) reported that their study “shows only a slight, if any, deleterious effect on early pregnancy” of harmaline in mice, and “tranylcypromine, like harmaline, is devoid of any appreciable deleterious effect on pregnancy.” In rats, Kamel and colleagues (1971) reported several abortifacient effects after the administration of a 2:1 mixture of harmine and harmaline, and Halky (1974) related poor reproductivity after DMT administration. These limited studies are

inconclusive, since some show toxic effects and others do not. Moreover, inconsistent results were found across studies, suggesting the possibility of interspecies differences, and putting at issue the studies’ relevance to humans.

The preclinical data received renewed evidence with the study by Oliveira and coworkers (2010). Ayahuasca was administered to pregnant rats in three different doses: an equivalent typical dose to that administered to humans, five times this dose, and ten times this dose, during the entire gestational period. The highest ayahuasca dose produced maternal toxicity, with decrease of weight gain and food intake. The study also reported visceral fetal findings like dilated brain lateral ventricle in the high-dose group, and dilated brain third ventricle and renal pelvis in all treatment groups, and these effects were dose dependent. Skeletal findings like incomplete ossification of the nasal bone were significantly increased in the high-dose group. The incidences of cervical rib, asymmetrically shaped sternbra, and incomplete ossification of hyoid bone, were significant in all treatment groups. Moreover, fetuses deriving from the highest dose group also presented a decrease in body weight.

However, as pointed out in detail by dos Santos (2010b), the frequency of ayahuasca administration and the high doses of one of the alkaloids (harmaline) used in this study were not of high relevance to the “real world” human ritual pattern of ayahuasca consumption, and cannot be meaningfully extrapolated to humans. In summary, the basic aspects pointed by dos Santos (2010b) were that:

- 1) The main toxicological findings were related to the higher doses;
- 2) The concentrations of harmaline were very high and out of the range normally found in ayahuasca preparations consumed in ayahuasca rituals by humans, and harmaline administered in high doses demonstrated selective neurotoxic effects in rats (Miwa et al. 2006; O’Hearn & Molliver 1997; O’Hearn & Molliver 1993). Nevertheless, lower doses of harmaline produced less severe and more inconsistent results in rats and it is very important to note that low and high doses of harmaline did not produce any neurotoxic effects in mice, suggesting that the neurotoxic effects of harmaline are species-specific;
- 3) Pregnant rats were exposed to ayahuasca throughout their entire pregnancy period, which is not especially relevant to the ritual pattern of ayahuasca consumption by pregnant women. As could be observed during personal field observations performed in the last decade, this particular group of ayahuasca consumers usually does not drink ayahuasca daily during all their pregnancy period and, in fact, they drink lesser amounts of the brew during the rituals (see also Labate 2011).

Different drugs, species and doses: some controversies. dos Santos (2010b) also pointed out some of the limitations of extrapolating preclinical data on drug toxicology

to the human realm, and to the ritual use of ayahuasca in particular. Metabolic and biochemical factors, for example, can be very different among species, and can produce important influences in the toxicology of drugs, as can dose, frequency and duration of drug administration.

A recent case which exemplifies the limitations of extrapolating preclinical data to humans is that of the empathogen-entactogen 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"). Although some doses and some administration schedules have demonstrated neurotoxic potentials in preclinical studies, the occurrence and demonstration of this neurotoxic potential in humans is still very controversial. Despite many methodological limitations that will not be discussed in the present text, it is very important to observe that the limitations of extrapolating animal data to humans are one of the main pillars of this debate (Mueller et al. 2012, 2011; Green et al. 2012, 2009; Halpern et al. 2011; de la Torre, Puerta & Aguirre 2009; Selvaraj et al. 2009; Lyvers 2006; de la Torre & Farré 2004; Vollenweider et al. 2001, 1999).

de la Torre & Farré (2004) argue that differences in the enzyme responsible for the metabolism of MDMA may cause different susceptibilities to neurotoxic effects in different species: while in humans this enzyme is CYP2D6, which is the same enzyme that metabolizes the ayahuasca alkaloids harmine and harmaline (Zhao et al. 2011; Wu et al. 2009; Callaway 2005; Riba et al. 2003; Yu et al. 2003); in rats the enzyme is CYP2D1, which, although analogous to the human CYP2D6, is not functionally identical (see also Mueller et al. 2012; Green et al. 2012; de la Torre, Puerta & Aguirre 2009). Furthermore, different specialists suggest that interspecies scaling methods have important limitations (Green et al. 2012, 2009; de la Torre, Puerta & Aguirre 2009; Lyvers 2006; Vollenweider et al. 2001, 1999).

Moreover, there is evidence of differences among species in the 5-HT_{2A/2C} receptors, which are involved in the effects of DMT (Dougherty & Aloyo 2011; Smith et al. 1998; McKenna & Peroutka 1989). Differences among species in the metabolic pathways involved in the biotransformation of harmine and harmaline were also reported (Zhao et al. 2012).

In this regard, it is plausible to speculate that all these interspecies biological differences may influence the toxic effects of different drugs, including ayahuasca, depending of the species, the dose, and the pattern of drug administration.

Recent advances. In a recent work, Oliveira and collaborators (2011) evaluated the neurobehavioral, reflexological and physical development of the rat offspring exposed to ayahuasca during pregnancy and lactation (from the sixth day of pregnancy to the tenth day of lactation). They administered the lowest dose used in their previous study (Oliveira et al. 2010). Ayahuasca did not induce maternal toxicity and did not alter physical and reflexological parameters or body weight. Ayahuasca also did

not alter both catalepsy and stereotyped behavior, but indicated that the animals were more sensitive to convulsant stimuli, probably explained by dopaminergic activity, since dopamine levels were found to be altered in the cortex of the experimental group. Nevertheless, no alterations were observed at central monoamine activity systems as determined by relations between metabolites and neurotransmitters. On the other hand, ayahuasca produced anxiolytic-like effects, as reflected by an increase in frequency of entries in open arms in the elevated plus-maze test. These data suggest that using a lower dose of ayahuasca, more similar to the doses typically consumed ritually by humans, reduces the toxic impacts of the brew.

Social aspects. In the case of ayahuasca, it is acknowledged that basic and preclinical research must be done, especially considering that thousands of people drink ayahuasca in Brazil alone (Labate, Rose & dos Santos 2009), including pregnant women. However, from a social perspective, despite the fact that syncretic religious manifestations with trance/possession-like rituals are common in many parts of the world where ayahuasca is used (such as in South American countries) it should be noted that western society does not have positive opinions about drug use in general, so ayahuasca users are seen with prejudice because they use a hallucinogenic (drug) plant preparation in their religious rituals (Labate 2011).

Scientists should be aware that their publications have social impact. It is very important when publishing scientific information that can potentially be used to increase prejudice against minorities to take caution and to point out very carefully the limitations of extrapolating preclinical toxicological data to humans (Labate 2011).

FINAL CONSIDERATIONS

The scientific literature reviewed above suggests that acute ayahuasca administration to healthy volunteers is relatively safe. The literature also gives support to the idea that long-term ritual ayahuasca consumption by adults and adolescents does not appear to be seriously toxic or harmful.

Although consumed ritually for at least some centuries, the available evidence derived from cross-sectional studies of adolescents who have chronically ingested ayahuasca and the interviews with mothers who used ayahuasca during pregnancy and did not report fetal death or abnormalities that they attributed to ayahuasca ingestion suggests that ayahuasca does not appear to be toxic to pregnant women or to their children. In this regard, the methodology used by Oliveira and coworkers should be applied to other species of animals (e.g., rabbits and dogs), also trying different frequencies of drug administration, and different doses. Scientists should acknowledge the limited relevance of preclinical nonhuman data to the "real world" human ritual use of ayahuasca.

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